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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,657	02/19/1999	PETER RUHDAL JENSEN	55411.000002	1335

21967 7590 03/11/2003

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	31

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,657	JENSEN ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a response, filed 1/3/03 as Paper No. 30, to the Notice of Non-responsive amendment mailed on 12/6/02 as Paper No. 29. The response points to support provided by the specification for the members of the Markush groups in pending claims 1 and 23, and overcomes an outstanding rejection against these claims for comprising new matter made in the office action mailed 2/28/02 as Paper No. 25.

Receipt is also acknowledged of two responses to the office action of Paper No. 25 (filed on 7/29/02 and 9/27/02 as Papers No. 27 and 28, respectively). These responses have amended several claims (claims 1, 16, 18, 21 and 23), and resulted in the cancellation of other claims (claims 24, 26 and 28). Claims 1-23, 25 and 27 remain pending and under consideration in the instant application. New rejections are made herein that were not necessitated by applicants' amendment of the claims in Papers No. 27 & 28. Therefore, this action is not final.

Claim Objections

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 19 recites the limitation that the increase in activity from one promoter sequence to at least one other promoter sequence of the set of promoter sequences of claim 18 is 50-100%. Claim 18 depends from claim 1, which already has the limitation that the change in activity between members of the promoter set occurs in steps of 50-100%. It would be remedial to simply delete this claim. **This is a new objection to the claims.**

Claim 20 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 20 recites the limitation that the selected organism of claim 18 is selected from the group consisting of a prokaryotic organism or a eukaryotic organism. Any organism selected for the method of claim 18 would necessarily be either eukaryotic or prokaryotic. It would be remedial to amend the claim to indicate the selected organism is one or the other, or to simply delete the claim. **This is a new objection to the claims.**

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 22 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 22 is directed towards a series of promoter sequences identified by a series of sequence identifiers. The specification does not appear to clearly indicate that each of the claimed promoter sequences is synthetically derived and does not exist in nature. The sequence listing identifies several, if not all, of the sequences recited in claim 22 as being obtained from a specific organism (e.g. L. lactis). Therefore, the claimed sequences appear to read on natural products and do not necessarily show the "hand of man" in their construction. Therefore, the instant claim has been rejected as directed towards non-statutory

subject matter. It would be remedial to amend the claim to read, "an isolated promoter sequence selected from the group consisting of".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 18-20, 23, 25 & 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection, necessitated by applicants' amendment of the claims in Papers No. 27 & 28.**

Claims 1-15, 23, 25 & 27 are drawn to a set of promoters suitable for optimizing expression of a gene in a selected organism or group of organisms wherein the set of promoters comprise at least two consensus sequences where at least half of the consensus sequences are kept constant across the promoter set. The set of promoters must cover "a range of activities" of "a" gene in small steps, each step changing the promoter activity by 50-100%. For prokaryotic promoters, the conserved sequences can be selected from the group consisting of TATAAT, TTGACA and an activator binding sequence upstream of the TATAAT sequence. For eukaryotic organisms, the at least two consensus sequences being selected from the group consisting of a TATA-box and a UAS upstream of the TATA-box, and where the promoter set further has a randomized spacer sequence between the two consensus sequences or flanking at

least one of the conserved sequences. Claims 18-20 are drawn towards methods of using subsets of promoter sequences obtained from the first set of promoter sequences to drive expression of a desired gene in an organism or groups of organisms, or to control the flux of a metabolite in the desired organism or group of organisms.

The rejected claims thus comprise a set of promoters that can be derived from any source to drive expression of any gene in any organism (e.g. humans, archaebacteria, etc.) or any combination of organisms (e.g. meeting the claim's functional limitations in both humans and fish, or humans and S. aureus). The upstream activator sequences can be literally of any type. The set of promoters must drive expression of the operably linked gene to a particular range of any possible range of activities. Functionally, the set of promoters must cover the range of expression in steps of 50-100%. Thus, the rejected claims encompass an incredibly enormous genus of promoter sets that must meet very specific functional limitations (i.e. expression of a gene in a particular organism, or combination of organisms, in steps of 50-100% change in activity levels). For example, the limitation of covering the range of expression in steps of 50-100%, greatly increases the description problems for the rejected claims. If one stipulates a single range of promoter activity for the claimed promoter set as from 1-100 units/hour, one can cover the range in steps of ~25 units/hour, ~10 units/hour, ~2 units/hour, etc. Thus, for every range of promoter activity, one can traverse the range in steps of 50-100% changes in activity in many different ways. Each of these different ways of traversing a given range of activity is likely to involve a series of different promoter constructs, each set possessing a different collection of promoters having different changes in the promoter sequence/structure. Given that the range of activities encompassed by the instant claims is any that is biologically possible, and

that the claims encompass regulating the expression of literally any gene in any single organism, or combination of different organisms, the genus of promoter sets encompassed by the rejected claims is so broad as to be incalculable.

The instant specification describes consensus promoter sequences observed in a few different prokaryotic or eukaryotic microorganisms (e.g. *L. lactis, E. coli, S. cerevisiae*) and describes experiments wherein a range of different promoter activities in different microorganisms is obtained. There is no description in the specification as originally filed of any promoter set that would meet the claim limitations in any particular multi-cellular organism (e.g. humans). While the range of activity obtained in some cases is impressive (e.g. Example1 and Figure 1), it is not clear from reading the examples and the legends to the figures that the promoter sets described necessarily meet the claim limitations (i.e. wherein half of at least two consensus sequences in at least two promoters in the library of promoters are conserved and wherein the at least two promoters only differ in activity by 50-100%). For example, the activities shown in Figures 1 & 3 are given on a logarithmic plot with no clear indicate that any two "adjacent" promoters necessarily meet the structural/functional limitations of the claim (e.g. on the logarithmic scale shown in these figures a difference in activity for "adjacent" promoters having 2-fold or 100% difference in activity cannot be clearly determined).

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of expression of a single gene in a single microorganism over, at best, a few possible ranges wherein the promoters within the set meet the functional limitations of the claims (e.g. a few possible subsets within the broader range of activities shown in Figure 1). The results

described are not necessarily predictive of promoter set structure for expression of different genes in the same organism (e.g. differences in transcription rates, transcript stability, etc.) or for the expression pattern of a given promoter set in a different organism. This is especially true for combinations of different organisms. For example, while certain promoter elements may be somewhat conserved across species lines (e.g. a TATA box), upstream activator binding sites of the invention would necessarily be expected to vary across species lines (e.g. human ans shrimp), making it impossible for one to extrapolate from the few promoters described herein those promoter sets that would necessarily meet the functional/structural characteristics of the rejected claims. The prior art also does not appear to provide a reliable basis for one of skill in the art to envision promoter sets that will necessarily meet the structural/functional limitations of the rejected claims for a given gene in an organism or groups of organisms.

There remains no structural/functional basis for one of skill in the art to envision those promoter sets that 1) retain the conserved sequences and 2) satisfy the functional limitations of the claim with regard to step-wise increments in promoter activity amongst the members of the promoter set for the incredibly broad genus of such promoter sets encompassed by the rejected claims (i.e. literally any combination of activity range, gene and organism, or combination of organisms). Therefore, one of skill in the art would not have been able to envision a representative number of specific promoter sets to describe the broad genus of promoter sets encompassed by the rejected claims. One of skill in the art would thus have reasonably concluded applicants were not in possession of the claimed invention for claims 1-15, 18-21, 23, 25 and 27.

Response to Arguments/112 1st Written Description

In Paper No. 27 applicants respond to a written description rejection of several of the claims that is similar to the one outlined above. Applicants' arguments presented in Paper No. 27, filed 7/29/02, have been considered but are not persuasive. The response in Paper No. 27 essentially argues: 1) the ordinary skilled artisan would understand that applicants were in possession of the claimed invention, as indicated by the examiner's appreciation of the full scope of the claimed invention, 2) to identify conserved promoter sequences is well within the common knowledge of the art and the measures required to carry out such identification are not dependent upon the particular type of organism, 3) the selection of such a set of promoters does not require any inventive skills but can be performed using conventional methods, 4) the invention does not lie primarily in the construction of the set of claimed promoters but in the realization by the inventors of how to construct such promoter sets by randomly changing sequences within spacer regions and that an optimized promoter is not necessarily the one exhibiting the highest level of expression, 5) applicants' specification provides a representative number of embodiments of the claimed promoter sets (e.g. Examples 1 & 2), 6) methodologies are provided for constructing similar promoter sets in other organisms (e.g. use of a B-galactosidase reporter for promoter activity), and 7) to deny applicants a patent because their invention may be applied to any organism is to deny them a patent because their invention is too effective and useful.

At no point has the examiner asserted that applicants' invention was not described because it is purportedly useful in any invention. The basis for the written description rejection was and remains that applicants have not presented a representative number of promoter sets sufficient to describe the claimed genus of promoter sets, or provided a basis for one of skill in

the art to envision a representative number of such promoter sets. As indicated above, a few examples that do not even clearly indicate that the promoter sets described in the invention necessarily meet the structural/functional limitations of the claims cannot be considered representative of the huge number of completely different promoter sets encompassed by the rejected claims. Applicants' realizations regarding how to construct the claimed promoter sets or the utility of an "optimal" promoter that is not the absolutely most prodigious promoter are irrelevant to the instant rejection in that the rejected claims are not directed towards methods of making the promoter sets. Arguments directed towards methodologies for constructing promoters that would be encompassed by the rejected claims would be better directed towards an enablement rejection of the claims. Neither applicants' response, the instant specification nor the prior art provide a basis for one of skill in the art to envision what the particular structures of promoters within promoter sets encompassed by the claims would necessarily look like in order to meet the specific functional limitations of the claims. Therefore, one of skill in the art would have reasonably concluded applicants were not in possession of the claimed invention at the time of filing.

Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments featuring promoter sets that regulate expression of a desired gene in an organism, does not reasonably provide enablement for any embodiment wherein the flux of a cellular metabolite is controlled. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims. **This is a new rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is complex, involving the generation of promoter sets that are functional in an organism to regulate expression a given gene so as to control the flux within the organism of a cellular metabolite. In order to construct promoter sets to use in the claimed method one must understand the effect of the desired gene on cellular metabolism for the desired host cell of a particular metabolite. This effect is greatly increased when the cell is located within a higher-level or multi-cellular organism where systemic physiology must be taken into account.

Breadth of the claims: The great breadth of the claims only exacerbate the complexity of the invention. The claims encompass promoter sets that are to be functional in any organism (e.g. human, rice, mouse, alfalfa, sea slug, etc.), microbial or multi-cellular, for the expression of any gene from any source over any given range of promoter activity. The limitation where a promoter of the invention is used to control the "flux" of any metabolite in an organism of any type greatly exacerbates the complexity of the invention, requiring, at a minimum, a knowledge of the metabolic physiology at the cellular level of literally any metabolite in any host organism, or combination of organisms.

Guidance of the specification/Existence of Working Examples: The teachings of the instant specification are directed exclusively towards microbial promoters and upstream

regulatory elements (e.g. in *S. cerevisiae* or *L. lactis*). There are no teachings, for example, for constructing promoter sets in multi-cellular organisms that meet the functional limitation of step-wise increments of promoter activity of 50-100% within that multi-cellular organism, much less in combinations of such higher organisms. There is no teaching of constructing promoter sets for the regulation of the cellular flux of a particular metabolite in any organism, much less a multi-cellular organism where systemic physiology will play a role in the flux of the metabolite in the organism. There are no working examples directed to controlling the "flux" of any particular metabolite in any particular organism.

State of the art/ Predictability of the art: The art of metabolic engineering is not predictable. In a review of the art concerning the metabolic engineering, Bailey teaches that there are a large number of variables that must be considered in making recombinant microorganism that produce a desired metabolite in a desired manner (Science, Vol. 252, pages 1668-1675; see the entire reference). These factors include, among others, how the gene is expressed in the cell, protein stability for the expressed gene product, and the global effects of the expression of the protein on the host cell (e.g. page 1674, final paragraph). For example, expression of even low concentrations of unnatural proteins can activate stress response, influencing many cell functions. Bailey concludes, "Although some of the experimental and mathematical tools required for rational metabolic engineering are available, complex cellular responses to genetic perturbations can complicate predictive design." (Abstract). The state of the art for practicing the claimed invention in multicellular organisms (e.g. humans, rice, etc.) would necessarily be even more unpredictable in that systemic physiology involving multiple tissue types would need be taken into account in practicing the invention in a predictable manner.

The amount of experimentation necessary: Given the factors outlined above, and the unpredictability of the art, it would have required undue trial-and-error experimentation of an unpredictable nature for one skill in the art to practice the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21, 23, 25 & 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "said promoter sequences covering a range of promoter activities for said gene in small steps each step changing the activity by 50-100%..." are unclear. Does the phrase mean that the range of activities occurs necessarily in the host organism, or can it occur in a cell in another type? For example, in embodiments where the organism(s) is multicellular (e.g. a human), can the step-wise promoter activity be determined in a microorganism (e.g. E. coli)? It would be remedial to amend the claim language to clearly indicate whether the cell in which the promoter activity is determined necessarily is the same as the recited organism(s). **This is a new rejection.**

Claim 1 is vague and indefinite in that it is unclear whether the sentence "...between said consensus sequences or flanking .....consisting of the nucleobases A, T, C and G..." refers to both eukaryotic and prokaryotic promoter sets of the invention, or only to the eukaryotic promoter sets. In general claim 1 suffers from having the prokaryotic and eukaryotic elements lumped together. It would be helpful to amend the claim structure such that the eukaryotic and

prokaryotic elements are clearly separated and so that those limitations which refer to both types of promoter sets clearly related to both types. For example, prokaryotic set limitations could be placed under element (a) and the eukaryotic limitations placed under (b), with limitations directed at both elements specifically addressing both (a) and (b).

Claim 16 is vague and indefinite in that the metes and bounds of the words "or both" in part (i)-line 5 are unclear. Do the words refer to both a selected organism and selected organisms? Or does it refer to the presence of non-conserved nucleotide spacer sequences flanking both of the two conserved sequences? Also, it is unclear how both the conserved promoter sequences can be "flanked" by "spacer" sequences when the specification appears to define spacer sequences as sequences between the two conserved sequences of promoter regions of the invention. **This is a new rejection.**

Claim 16 is vague and indefinite in that there is no clear and positive prior antecedent basis for the words "the set of promoter sequences covering a range of promoter activities for said gene". **This is a new rejection.**

Claim 17 is vague and indefinite in that it merely recites a desired outcome (i.e. "wherein the set of promoter sequences obtained spans, with respect to promoter activities for said gene, the range in steps, each step changing the activity by 50-100%") without any action steps that would necessarily give the desired result. There is no step, as the claim is currently written, in the method of claim 17 that would necessarily result in obtaining the set of promoters produced by the method of claim 16, upon which claim 17 depends, that would necessarily yield a set of promoter sequences that spanned a range of activity for the expression of the desired gene in steps of 50-100% across the set of promoters. **This is a new rejection.**

Claim 18 is vague and indefinite in that there is no clear and positive prior antecedent basis for the words "the B-galactosidase activity" in the claim, or in claim 1, upon which claim 18 is dependent. Also, there is no clear and positive prior antecedent basis for the words "said gene" in line 1 of part (i) of the claim. Claim 1, upon which claim 18 is dependent, merely recites the limitation of "a gene" without specifying a specific gene. There is no language in claim 18 that specifically links the gene of claim 1 with that recited in the preamble of claim 18. **These are new rejections, necessitated by applicants' amendment of the claims.**

Claim 21 is vague and indefinite in that there is no clear and positive prior antecedent basis in claim 21 for the words "the B-galactosidase activity" in claim 21, or in claim 16, upon which claim 21 is dependent. Also, there is no clear and positive support in the claim for the phrase "the at least one gene in the pathway or the gene expressing the desired gene product" or the phrase "a higher or lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product" in claim 16, upon which claim 21 is dependent. **This is a new rejection.**

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
March 9, 2003